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(54) Title: DENTIFRICE COMPOSITIONS

(57) Abstract: The present invention relates to a dentifrice composition comprising first and second constituents susceptible to inter-reaction with one another, wherein said constituents are in admixture with one another but at least one of said constituents is in an activity resistant particle form that resists such inter-reaction until the composition is used.

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DENTIFRICE COMPOSITIONS

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DESCRIPTION

Technical Field

This invention relates to dentifrice compositions.

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Background Art

Many compounds are known to be useful for cleaning teeth and/or for preventing tooth decay and/or for treating gum disease, but they are applied topically (e.g. by a qualified person) in a dental surgery and are not generally available in a dentifrice composition suitable for use by individual patients or members of the public at large. This is because it is difficult to incorporate many of such known active compounds satisfactorily into a suitable carrier compound. For example, a particularly active compound such as cetylpyridinium chloride (a known anti-plaque agent hereinafter called ACPC@) breaks down or becomes inactive when mixed in a conventional toothpaste carrier gel, and triclosan and bromochlorophene discolour and/or give loss of clarity to an otherwise clear carrier gel as might be used in a conventional toothpaste.

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Summary of the Invention

With a view to overcoming or at least reducing these difficulties, the present invention contemplates the provision of a dentifrice composition comprising first and second constituents susceptible to inter-reaction with one another, wherein said constituents are in admixture with one another but at least one of said constituents is in an activity resistant particle form that resists such inter-reaction until the composition is used.

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Preferably said activity resistant form comprises a micro-encapsulated environment or a so-called "ingredient pearl" or "unisphere" environment. Advantageously, said environment provides the said at least one of the constituents as a substantially immobile part of a solid matrix.

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The, or at least one of the, constituents in the micro-encapsulated, ingredient pearl or unisphere environment may be soluble in or softened by water and/or saliva so as to permit breakdown of the said environment when the dentifrice is used. For example the matrix particle may be softened by water and/or saliva such as to relinquish its barrier effect (and permit reactive mobility of the said at least one of the constituents) by abrasion, e.g. as by use in brushing of the teeth.

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As used hereinafter, the micro-encapsulated environment will be referred to as a "unisphere". This term will be used hereinafter to refer to the particles/pellets that contain the said first constituent in an environment away from said second constituent.

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Detailed Description of the Invention

In a preferred embodiment of the present invention, the unisphere is formed from the at least one said constituent and at least one additional component selected from gelatin, alginate, gum acacia, cellulose, lactose, microcrystalline cellulose, cellulose ether and hydroxypropyl methylcellulose or mixtures thereof. Preferably, the at least one additional component is microcrystalline cellulose, cellulose, cellulose ether or lactose.

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The first constituent is a dentifrice active agent, preferably cetylpyridinium chloride.

In accordance with a preferred embodiment, the unispheres have a diameter within the range of from 0.1mm to 3mm, more preferably within the range of from 0.5mm to 0.9mm or within the range of from 0.9mm to 1.5mm.

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The dentifrice composition of the present invention may be in the form of a solid or liquid dentifrice such as a toothpaste, mouthwash, paste and the like. Most preferably the composition is in the form of a toothpaste and the second constituent of the composition is therefore a carrier gel. Said gel may comprise one or more of
5 surfactants, cleaning agents, fluoride containing agents, anti-plaque agents, gelling agents, thickeners, sweetners, colouring agents, preservatives, anti-bacterial agents and anti-tartar agents. Such toothpaste carriers are well known in the art, further details of the constituent components is provided below.

10 Compositions in the form of toothpastes, denture cleansing liquids and pastes and the like will generally comprise a binder or thickening agent. Binders suitable for use herein include carboxyvinyl polymers, carrageenan, hydroxyethyl cellulose and water soluble salts of cellulose ethers such as sodium carboxymethyl cellulose and sodium carboxymethyl hydroxyethyl cellulose. Natural gums such as gum karaya,
15 xanthan gum, gum arabic, and gum tragacanth can also be used. Sodium aluminum silicate, magnesium aluminum silicate or other silicates such as finely divided silica can be used as part of the thickening agent to further improve texture. Binders/thickening agents can be used in an amount from about 0.1% to about 5.0%, preferably from about 0.1 to about 1% by weight of the total composition.

20 A soluble fluoride ion source can also be incorporated in the present compositions. The soluble fluoride ion source is used in amounts sufficient to provide from about 50 to about 3500 ppm of the fluoride ion. Preferred fluorides are sodium fluoride, stannous fluoride, potassium fluoride, indium fluoride, ammonium fluoride,
25 ammonium bifluoride, zinc ammonium fluoride, tin ammonium fluoride, calcium fluoride, amine fluoride and sodium monofluorophosphate. Norris et al., U.S. Pat. No. 2,946,735, issued Jul. 26, 1960 and Widder et al., U.S. Pat. No. 3,678,154, issued Jul. 18, 1972 disclose such salts as well as others.

30 It is also desirable to include some humectant material in a toothpaste to keep the composition from hardening upon exposure to air. Certain humectants can also

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impart a desirable sweetness to toothpaste compositions. Liquid dentifrice and mouthwashes can also contain a quantity of humectant. Suitable humectants include glycerin, sorbitol, xylitol, polyethylene glycols, propylene glycol, other edible polyhydric alcohols, and mixtures thereof. When present, humectants generally represent from about 10% to about 70%, by weight of the compositions of the invention.

Toothpastes carriers will generally comprise an abrasive polishing material. The abrasive polishing material contemplated for use herein can be any material which does not excessively abrade dentin or denture acrylic. These include, for example, silicas including xerogels, hydrogels, aerogels and precipitates, calcium and magnesium carbonates, calcium ortho-, pyro-, meta- and polyphosphates such as dicalcium orthophosphate dihydrate, calcium pyrophosphate, tricalcium phosphate, and calcium polymetaphosphate, insoluble sodium polymetaphosphate, alumina and hydrates thereof such as alpha alumina trihydrate, aluminosilicates such as calcined aluminium silicate and aluminium silicate, magnesium and zirconium silicates such as magnesium trisilicate and thermosetting polymerised resins such as particulate condensation products of urea and formaldehyde, polymethylmethacrylate, powdered polyethylene and others such as disclosed in U.S. Pat. No. 3,070,510, Dec. 25, 1962. Mixtures of abrasives can also be used. The abrasive polishing materials generally have an average particle size of from about 0.1 to about 30 microns, preferably from about 5 to 15 microns.

Silica dental abrasives of various types offer exceptional dental cleaning and polishing performance without unduly abrading tooth enamel or dentin. The silica abrasive can be precipitated silica or silica gels such as the silica xerogels described in Pader et al., U.S. Pat. No. 3,538,230, issued Mar. 2, 1970 and DiGiulio, U.S. Pat. No. 3,862,307, Jun. 21, 1975, for example silica xerogels marketed under the tradename "Syloid" by W. R. Grace & Company, Davison Chemical Division. Suitable precipitated silica materials include those marketed by the J. M. Huber Corporation under the tradename, "Zeodent", particularly the silica carrying the

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designation "Zeodent 119". These silica abrasives are described in U.S. Pat. No. 4,340,583, Jul. 29, 1982.

Highly preferred herein from the viewpoint of providing good cleansing performance combined with excellent compatibility with the antiplaque agent are calcium carbonate abrasives.

The abrasive is generally present in dentifrice compositions of the invention at a level of from about 10% to about 70%, preferably from about 15% to about 25% by weight.

The present compositions can also contain surfactants. Suitable surfactants are those which are reasonably stable and foam throughout a wide pH range, including non-soap anionic, nonionic, cationic, zwitterionic and amphoteric organic synthetic detergents. Many of these suitable agents are disclosed by Gieske et al. in U.S. Pat. No. 4,051,234, Sep. 27, 1977.

Examples of suitable surfactants include alkyl sulfates; condensation products of ethylene oxide with fatty acids, fatty alcohols, fatty amides, polyhydric alcohols (e.g. sorbitan monostearate, sorbitan oleate), alkyl phenols (e.g. Tergitol) and polypropyleneoxide or polyoxybutylene (e.g. Pluronic); amine oxides such as dimethyl cocamine oxide, dimethyl lauryl amine oxide and cocoalkyldimethyl amine oxide (Aromox); polysorbates such as Tween 40 and Tween 80 (Hercules); sorbitan stearates, sorbitan monooleate etc; sarcosinates such as sodium cocoylsarcosinate, sodium lauroyl sarcosinate (Hamposyl-95 ex W. R. Grace); cationic surfactants such as cetyl pyridinium chloride, cetyl trimethyl ammonium bromide, di-isobutyl phenoxy ethoxy ethyl-dimethyl benzyl ammonium chloride and coconut alkyl trimethyl ammonium nitrate. A preferred surfactant is sodium laureth sulphate.

The present compositions can also include an anti-calculus agent. Suitable anti-calculus agents include the di- and tetra-alkali metal pyrophosphates as set out in

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EP-A-097476. Specific salts include tetra alkali metal pyrophosphate, dialkali metal diacid pyrophosphate, trialkali metal monoacid pyrophosphate and mixtures thereof, wherein the alkali metals are sodium or potassium. The salts are useful in both their hydrated and unhydrated forms. The amount of pyrophosphate salt useful in these compositions is any effective amount and is generally enough to provide in composition at least 1.0% P.sub.2 O.sub.7.sup.-4, preferably from about 1.5% to about 10%, more preferably from about 3% to about 6% by weight or composition. The pyrophosphate salts are described in more detail in Kirk & Othmer, Encyclopedia of Chemical Technology, Second Edition, Volume 15, Interscience Publishers (1968).

Other anti-calculus agents suitable herein are zinc salts. Zinc salts are disclosed in U.S. Pat. No. 4,100,269, U.S. Pat. No. 4,416,867, U.S. Pat. No. 4,425,325 and U.S. Pat. No. 4,339,432. A preferred agent of the zinc variety is zinc citrate. Zinc compounds can be present in amounts sufficient to provide from about 0.01% to about 4%, preferably from about 0.05% to about 1% by weight of zinc ion.

Other suitable anti-calculus agents include the synthetic anionic polymers (including polyacrylates and copolymers of maleic anhydride or acid and methyl vinyl ether (eg Gantrez) as described in U.S. Pat. No. 4,627,977, polyamino propane sulfonic acid, polyphosphates (eg tripolyphosphate, hexametaphosphate), diphosphonates (eg EHDP, AHP), polypeptides (eg polyaspartic and polyglutamic acids), and mixtures thereof.

Sweetening agents which can be used include aspartame, acesulfame, saccharin, dextrose, levulose and sodium cyclamate. Sweetening agents are generally used at levels of from about 0.005% to about 2% by weight of composition.

Other optional components for use herein include water-soluble antibacterial agents, such as chlorhexidine digluconate, quaternary ammonium antibacterial compounds and water-soluble sources of certain metal ions such as zinc, copper, silver and

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stannous (e.g., zinc, copper and stannous chloride, and silver nitrate); pigments such as titanium dioxide; orally acceptable dyes/colorants such as FD&C Blue #1, FD&C Yellow #10, FD&C Red #40; antioxidants, vitamins such as vitamin C and E, other antiplaque agents such as stannous salts, copper salts, strontium salts and magnesium salts; pH adjusting agents, anticaries agents such as urea, calcium glycerophosphate, sodium trimetaphosphate, plant extracts, desensitizing agents for sensitive teeth such as potassium salts e.g. chloride, nitrate or citrate, and mixtures thereof.

10 If in the form of a mouthwash, the second constituent is a liquid carrier such as a mouthwashes water/alcohol solution comprising flavor, humectant, sweetener, sudsing agent, and colorant as described above. Mouthwashes can include ethanol at a level of from 0 to 60%, preferably from 5 to 30% by weight.

15 Denture cleanser compositions of the invention can additionally include one or more bleaching agents, organic peroxyacid precursors, effervescence generators, chelating agents, etc

20 The bleaching agent may take the form of an inorganic persalt and can be selected from any of the well-known bleaching agents known for use in denture cleansers such as the alkali metal and ammonium persulfates, perborates, percarbonates and perphosphates and the alkali metal and alkaline earth metal peroxides. Examples of suitable bleaching agents include potassium, ammonium, sodium and lithium persulfates and perborate mono- and tetrahydrates, sodium pyrophosphate
25 peroxyhydrate and magnesium, calcium, strontium and zinc peroxides. Of these, however, the alkali metal persulfates, perborates and mixtures thereof are preferred for use herein, highly preferred being the alkali metal perborates. Indeed, it is a feature of the invention that the tablet compositions herein will provide excellent antimicrobial activity even in the absence of alkali metal persulfates.

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The amount of bleaching agent in the total composition is generally from about 5 to

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about 70% preferably from about 10% to about 50%. In compositions comprising a mixture of alkali metal persulfates and perborates, the overall persulfate:perborate ratio is suitably from about 5:1 to about 1:5, more especially from about 2:1 to about 1:2.

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The denture cleansing compositions can also incorporate an effervescence generator, ie a material which in the presence of water releases carbon dioxide or oxygen with effervescence. The effervescence generator can be selected from generators which are effective under acid, neutral or alkaline pH conditions, but preferably it consists of a combination of a generator which is effective or most effective under acid or neutral pH conditions and a generator which is effective or most effective under alkaline pH conditions. Effervescence generators which are effective under acid or neutral pH conditions include a combination of at least one alkali metal carbonate or bicarbonate, such as sodium bicarbonate, sodium carbonate, sodium sesquicarbonate, potassium carbonate, potassium bicarbonate, or mixtures thereof, in admixture with at least one non-toxic, physiologically-acceptable organic acid, such as tartaric, fumaric, citric, malic, maleic, gluconic, succinic, salicylic, adipic or sulphamic acid, sodium fumarate, sodium or potassium acid phosphates, betaine hydrochloride or mixtures thereof. Of these, malic acid is preferred. Effervescence generators which are effective under alkaline pH conditions include persalts such as alkali and alkaline earth metal peroxoborates as well as perborates, persulphates, percarbonates, perphosphates and mixtures thereof as previously described, for example, a mixture of an alkali metal perborate (anhydrous, mono- or tetrahydrate) with a monopersulphate such as Caroat.RTM. marketed by E I du Pont de Nemours Co. and which is a 2:1:1 mixture of monopersulphate, potassium sulphate and potassium bisulphate and which has an active oxygen content of about 4.5%.

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Examples of suitable cleaning agents include alkali metal orthophosphates such as monosodium phosphate, disodium phosphate or trisodium phosphate, alkali metal

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citrates, sodium bicarbonate or combinations thereof as known in the art with care to avoid the known unstable combinations of these components.

5 The unispheres may be coloured decorative items and/or may comprise one or more active ingredients.

10 In the most preferred embodiments of the invention the dentifrice composition is in the form of a toothpaste comprising a translucent, substantially clear, gel of a suitable food grade colour containing, e.g. at levels between 0.2% and 1.0% w/w, unispheres containing CPC. Such a gel may have the following formulation:

	Sorbitol	37.0 - 75.0% w/w
	Water	5.0-45.0% w/w
	Hydrated Silica or Silica	15.0-30.0% w/w
	Glycerin	5.0-20.0% w/w
15	Flavour	0.5 - 1.2% w/w
	Sodium Laureth Sulfate or Cocamidopropyl Betaine	0.5 - 2.0% w/w
	Aloe Vera	0.05-10.00% w/w
	Cellulose Gum	0.2-2.0% w/w
	Allantoin	0.05-0.50% w/w
20	Sodium Lactate	0.1-5.0% w/w
	Sodium Fluoride or Sodium Monofluorophosphate	max. of 1 500ppm F
	Lactic Acid	for a pH range of 5.0 - 7.5
	Sodium Saccharin	0.05-0.30% w/w
	Sodium Hydroxymethylglycinate	max. of 0.5% w/w.

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Suitable unispheres may be obtained from Induchem AG, Industriestrasse 26, 8604 Volketswil, Switzerland.

30 The manufacturing process for the particles preferably comprises the sequential steps of:

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- (a) initially mixing together and blending, as pre-weighed constituents, the active ingredient CPC with cellulose, cellulose ether, lactose, and any desired pigments, to form a homogenous premix or matrix,
- (b) pelletising the premix to form pellets
- 5 (c) rendering the pellets substantially spherical in form - so called spheronising -
- (d) drying the spheronised pellets in a fluid bed dryer,
- (e) fractionising the dried pellets to provide particles of desired size.

These particles are then blended with the gel to form the final composition that, at a filling station, is dispensed into tubes or other containers for the dentifrice composition.

The production process, and the several compounds selected for admixture, provide for the resultant particles or pellets to have the active ingredient (CPC) trapped and rendered immobile by the substantially longer chain molecular form of the other pellet constituents. These longer chain molecules have relatively weak bonds and are physically broken down by abrasion of the particle-surface — as arises by brushing of the teeth with the dentifrice composition that has these particles randomly embedded in the carrier gel. The released CPC can then go into solution with oral saliva and become active as an anti-plaque agent.

It will be appreciated that other dentifrice compositions may be provided whilst still according to the present invention. For example, the particles or so-called capsules may be made from Gelatin, Alginate, Gum Acacia, Cellulose, Lactose and Hydroxypropyl Methylcellulose or any combination thereof, and in any food grade colour.

The particles or capsules may contain a wide variety of materials and indeed may even be in the form of empty capsules (i.e. with no active ingredient) for visual appeal only. Suitable contents for the particles or capsules may include: vitamins and essential oils - for marketing claims (e.g. "Contains X") - and/or active ingredients that could not otherwise be added to clear gel dentifrices or toothpastes,

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either for loss of clarity (e.g. Triclosan or Bromochlorophene) or due to the inactivation of the active ingredients (e.g. Cetylpyridinium Chloride). Indeed a number of different compounds, each separately micro-encapsulated, may be included in the one dentifrice composition.

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It will further be appreciated that micro-encapsulation of one or more constituents of a dentifrice composition in accord with the present invention offers a number of advantages. These include:

- (1) The ability of the microcapsules to provide gentle abrasion of the teeth,
- 10 (2) Visual appeal of the dentifrice composition having the microcapsules visible within the clear gel,
- (3) Isolation of the reactive ingredients within the microcapsules rendering them non-reactive with the gel (or one another) until the composition is used and the encapsulated matrix is broken down, the active ingredient
15 (cetylpyridinium chloride) being therefore stabilised in respect of the remaining components
- (4) Incorporation of insoluble active ingredients in gel formulations, and
- (5) Controlled release of active ingredients.

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Other modifications and embodiments of the invention, which will be readily apparent to those skilled in this art, are to be deemed within the ambit and scope of the invention, and the particular embodiment(s) hereinbefore described may be varied in construction and detail, e.g. interchanging (where appropriate or desired) different features of each, without departing from the scope of the patent monopoly
25 hereby sought.

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CLAIMS

1. A dentifrice composition comprising first and second constituents susceptible to inter-reaction with one another, wherein said constituents are in admixture with one another but at least one of said constituents is in an activity resistant particle form that resists such inter-reaction until the composition is used.
2. A composition according to claim 1, wherein the activity resistant particle form is a unisphere.
3. A composition according to claim 2, wherein the unisphere is formed from the at least one said constituent and at least one additional component selected from gelatin, alginate, gum acacia, cellulose, lactose, microcrystalline cellulose, cellulose ether and hydroxypropyl methylcellulose.
4. A composition according to claim 3, wherein the at least one additional component is microcrystalline cellulose, cellulose, cellulose ether or lactose.
5. A composition according to claim 3 or 4, wherein the at least one said constituent is cetylpyridinium chloride (CPC).
6. A composition according to any preceding claim, wherein the unispheres have a diameter within the range of from 0.1mm to 3mm.
7. A composition according to claim 6, wherein the unispheres have a diameter within the range of from 0.5mm to 0.9mm.
8. A composition according to claim 6, wherein the unispheres have a diameter within the range of from 0.9mm to 1.5mm.

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9. A composition according to any preceding claim, wherein the second constituent is a carrier gel.
10. A composition according to claim 9, wherein said gel comprises one or more
5 of surfactants, cleaning agents, fluoride containing agents, anti-plaque agents, gelling agents, thickeners, sweeteners, colouring agents, preservatives, anti-bacterial agents and anti-tartar agents.
11. A dentifrice composition containing a stabilised form of cetylpyridinium
10 chloride whereby said cetylpyridinium chloride is only exposed to the majority of other compositional components upon use.
12. A composition according to claim 11, wherein the cetylpyridinium chloride is present in unispheres.
15
13. A composition according to claim 12, wherein the unispheres are formed from cetylpyridinium chloride and at least one additional component selected from gelatin, alginate, gum acacia, cellulose, lactose, microcrystalline cellulose, cellulose ether and hydroxypropyl methylcellulose.
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14. A composition according to claim 12, wherein the at least one additional component is microcrystalline cellulose, cellulose, cellulose ether or lactose.
15. A composition according to claim 14, wherein the unispheres have a
25 diameter within the range of from 0.1mm to 3mm.
16. A composition according to claim 15, wherein the unispheres have a diameter within the range of from 0.5mm to 0.9mm.

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17. A composition according to claim 15, wherein the unispheres have a diameter within the range of from 0.9mm to 1.5mm.

18. Use of a unisphere comprising cetylpyridinium chloride and at least one additional component selected from gelatin, alginate, gum acacia, cellulose, lactose, microcrystalline cellulose, cellulose ether and hydroxypropyl methylcellulose in the manufacture of a dentifrice composition.

19. Use according to claim 18, wherein the at least one additional component is microcrystalline cellulose, cellulose, cellulose ether or lactose.

20. Use according to claim 18 or 19, wherein the unispheres have a diameter within the range of from 0.1mm to 3mm.

21.. Use according to claim 20, wherein the unispheres have a diameter within the range of from 0.5mm to 0.9mm.

22. Use according to claim 20, wherein the unispheres have a diameter within the range of from 0.9mm to 1.5mm.

23. Method of stabilising cetylpyridinium chloride in a toothpaste comprising (a) preparing the cetylpyridinium chloride in the form of unispheres and (b) admixing said unispheres with a carrier gel.

INTERNATIONAL SEARCH REPORT

Internat'l Application No
PCT/GB 00/02833

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K7/16		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) WPI Data, PAJ, EPO-Internal		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 11754 A (PROCTER & GAMBLE) 24 June 1993 (1993-06-24) claims; example 1 ---	1-23
X	US 5 300 305 A (STAPLER JUDITH H ET AL) 5 April 1994 (1994-04-05) claims; example 1 ---	1-23
X	US 4 071 614 A (GRIMM III JOHN EDWARD) 31 January 1978 (1978-01-31) claims 1,11 -----	1-23
<input type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center; font-weight: bold;">3 November 2000</div>		Date of mailing of the international search report <div style="text-align: center; font-weight: bold;">10/11/2000</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center; font-weight: bold;">Beys, E</div>

INTERNATIONAL SEARCH REPORT

Information on patent family members

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